

07/949,652

09/13/94

SIGNATURE


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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

1807

ART UNIT

PAPER NUMBER

18

DATE MAILED: 11-13-94

 This is a communication from the examiner in charge of your application.
 COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined
 ☒ Responsive to communication filed on 8-8-94
 ☒ This action is made final

 A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
 Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-16, 21-27, 37, and 39-43 are pending in the application.
 Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 17-20, 28-36, and 38 have been cancelled.
3. ☒ Claims 21-27, 37, and 39-43 are allowed.
4. ☒ Claims 1-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other _____

EXAMINER'S ACTION

MISCELLANEOUS

1. Acknowledgement is made of the filing of the response and amendment of July 18, 1992 as well as the supplemental response and Declaration filed on August 8, 1994. NOTE: At pages 4-5 of the amendment filed July 13, 1994, there appears a request
5 for the entry of new claims 17-20 and 35-38. This portion of the amendment has NOT been entered as said claims have been previously cancelled. Accordingly, claims 1-16, 21-27, 37, and 39-43 are currently pending.

2. The objections to the specification as it relates to (i) the citation of references which have been incorporated by reference and (ii) the current status of cited
10 applications, have been withdrawn in view of applicant's remarks and the amendments to the specification.

3. The objection to the abstract has been withdrawn in view of the amendment to same.

4. The rejection of claims 1-16 under 35 U. S. C. § 112, first paragraph, as it
15 relates to issues of new matter has been withdrawn in view of applicant's remarks as found on pages 8-10 of the response filed July 13, 1994.

5. The rejection of claims 1-16, 26, 27, 37, and 39-43 under 35 U. S. C. § 112, second paragraph, has been withdrawn in view of applicant's remarks and the amendments to the claims.

REJECTION UNDER 35 U. S. C. § 112, FIRST PARAGRAPH

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or
25 with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i. e., failing to provide an enabling disclosure.

Claims 1-13, 15, and 16 are not enabled by the specification for a generic method
5 of detecting at least one coding region allele of a multi-allelic genetic locus. The specification teaches the determination of the likelihood of a criminal suspect as being implicated in a crime and the parentage of a child wherein in both instances the RFLP pattern for HLA locus was analyzed. The specification does not provide sufficient enablement such that one of skill in the art would be able to detect at least one coding
10 region allele of any multi-allelic genetic locus where the genomic DNA can be derived from virtually any source. In particular, the specification has not provided guidance as to how one is to predetermine what types of primers (sequence length and composition) are to be used given the generic applicability of the claimed method to a variety of loci. This aspect is further complicated when one considers that a given
15 locus may well be comprised of a cluster of alleles (*exempli gratia* the HLA Class II locus DQA1 is comprised of 8 alleles and the DPB locus is comprised of 24 alleles).

The specification is not enabling for the generation and use of primers that would be of sufficient length such that they permit the spanning of virtually any intronic sequence. To this end, applicant's attention is directed to the publication of
20 Padgett *et al.*, where on page 1124, second paragraph, it is stated: "The length of introns in vertebrate genes ranges from approximately 50 to well over 10,000 bases with no obvious periodicity." While this publication only makes reference to that encountered in vertebrates, the claimed method has sufficient breadth of scope so as to permit the inclusion of invertebrates as well as plants and fungi. Clearly, the
25 specification has not provided sufficient guidance as to the application of the instantly claimed method to "for detection of at least one coding region allele of a multi-allelic genetic locus" which entails the use of a "primer pair that spans a non-coding region sequence" where said non-coding region can be but is not limited to introns; see *supra*.

Claims 1-13, 15, and 16 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Applicant's argument

Applicant, at pages 11-12 of the response of July 13, 1994 asserts:

5 (i) "[T]he application provides pages of guidance as to the selection of primers of appropriate length and composition. In particular, page 13, line 15 through page 24, line 36, describes the selection of primers, including sections describing the length of the resultant amplified sequences, the location of the amplified sequences, and the required length and sequence homology of primers" (page 11).

10 Applicant's remarks have not been found to be persuasive for while limited agreement is reached in that one of skill in the art may be able to develop primers and probes, there is however a low level of predictability of achieving a useful probe or primer such that one would be able to practice the claimed method in a general sense. As set forth in the above basis of the rejection, it is accepted in the art that the length
15 of intronic sequences which are encompassed by the generic heading of "non-coding regions" can be extensively long. The specification has not set forth a repeatable procedure whereby one of skill in the art would be able to readily produce primers and effectively amplify genomic DNA which entails regions of thousands of nucleotides in length. Concern over the upper limits of the length of the amplified sequence are
20 significant as fidelity and stability of the primary structure of the amplified DNA becomes suspect at such upper limits. In particular, it is well known in the art that when primers of approximately 20 or more residues are used and when the amplified DNA sequence is greater than several hundred bases in length, secondary structures may result in each of these critical components. The result of these secondary
25 structures being the claimed method rendered inoperable.

(ii) "At page 11, lines 31-33, the term 'intron spanning primers' is defined as 'a primer pair that amplifies at least a portion of one intron.' Therefore, since the primers amplify a portion of an intron, it is irrelevant whether the intron is 200

nucleotides or 10 kilobases in length since the method only need amplify a portion of the intron" (page 12).

5 Applicant's assertions are not persuasive for while the claims may well encompass the amplification of a part or portion of an intron, now a "non-coding region", the claims have sufficient breadth of scope to encompass the spanning of the complete length of the intron/non-coding region, as well as additional sequences. The specification clearly does not enable the use of primers which allow for the amplification of such large sequences.

10 Claim 14 remains rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to the detection of cystic fibrosis using the method steps recited in claims 7 and 13 taken with the use of the primers recited in Example 6 (pages 90-91 of the specification). It is noted with particularity that the specification only discloses the detection of cystic fibrosis in accordance with the method set forth in
15 Example 6 and that the specification does not present nor reasonably suggest any alternative method by which the method could be practiced with a reasonable expectation of success. See MPEP 706.03(n) and 706.03(z).

Re. Declaration of Dr. Peter Gresshoff

20 The declaration of Dr. Gresshoff, filed 23 September 1992 has been fully considered on the merits with the following effect:

The declaration is not persuasive for the opinion being presented lacks any showing of evidence to support same. It is noted with particularity that Dr. Gresshoff states at page 3, first paragraph, that he "identified a region of DNA sufficiently near
25 the gene so that recombination is very unlikely". However, it is not stated nor shown just what the sequence is, how the determination of it probability of recombination was determined, nor the methods used so to reach this determination. Also, at page 4, second

paragraph, the declarant states that "I found these additional data convincing for a number of reasons", however, nor data has been presented which would support the position being presented.

At page 4, last paragraph, it is stated that "although we have not sequenced the NTS gene, we believe it is a conserved gene . . ." (emphasis added), however, there is only one individual making the declaration. Accordingly, the aspect of who is forming the collective opinion is unclear. Further, it is not readily apparent just how one can effectively determine whether a gene is or is not conserved when one has not sequenced it. Accordingly, the aspect of the NTS gene being conserved and useful in the claimed method is unsupported opinion.

For the above reasons, and in the absence of convincing evidence to the contrary, the declaration of Dr. Gresshoff has not been found to be persuasive in overcoming the enablement rejection under § 112, first paragraph.

Re. Declaration of Leroy Hood

The 37 CFR § 1.132 declaration of Leroy Hood, filed September 28, 1993, has been fully considered with the following effect:

Agreement is reached in that the data presented in the specification supports the position that one can use relatively short non-coding region sequences in HLA typing (see Patent No. 5,192,659, claims 1-11), however, the declaration does not present any evidence or suggestion that the specification as originally filed enables one of skill in the art to practice the claimed method in a generic manner where the primer pair spans a non-coding region that could be many kilobases in length, e.g., 10 kb, and simultaneously develop primers that would allow for one of skill in the art to amplify any non-coding region sequence which is adjacent to an exon encoding the allele where the allele is part of a multi-allelic genetic locus.

At page 2, second paragraph, Dr. Hood states: "My data demonstrated a similar phenomenon between genes of species which diverged approximately seventy to

eighty million years ago", however, the declaration lacks any factual or evidentiary underpinning which would support the conclusory opinion being offered.

For the above reasons and in the absence of convincing evidence to the contrary, the declaration of Dr. Leroy Hood has not been found to be persuasive in
5 overcoming the rejection under § 112, first paragraph.

Re. Declaration of Pablo Rubinstein

The 37 C.F.R. § 1.132 declaration of Pablo Rubinstein, filed August 8, 1994, has been fully considered on the merits with the following effects:

At page 1, second paragraph, declarant states that he "previously submitted a
10 Declaration regarding Malcom Simon's discovery that one could use relatively short regions of non-coding sequences closely linked to a polymorphic gene to define the corresponding coding allele", however, a review of the record fails to produce any prior declaration from declarant.

At pages 2-3 of the declaration said declarant presents a review of several
15 publications. While agreement is reached in that since the filing of the subject application other polymorphic, multi-allelic loci have been identified, such a showing has not been found to support the position that the specification as originally found would enable one of skill in the art would be able to practice the claimed invention when any multi-allelic genetic locus is used. While the specification does identify a
20 variety of diseases and states that there are "[o]ther diseases which are believed to be monogenic for which the gene has not been identified", such a showing is considered only an invitation to experiment and not enablement.

In view of the foregoing remarks and in the absence of convincing evidence to the contrary, the declaration of Dr. Rubinstein has not been found to be persuasive in
25 overcoming the rejection under § 112, first paragraph.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Claims 1-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. patent no.

5 5,192,659. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application, which are broader in scope of that of said patent, are also drawn to a method for detecting at least one coding region allele of a multi-allelic genetic locus. NOTE, the HLA locus is comprised of approximately 50 alleles (see column 1, lines 60-63, of the patent). Given such a showing, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the claimed method of detection of at least one coding region allele of a multi-allelic genetic locus where the multi-allelic locus could be that of human leukocyte antigen (HLA) as recited in the patented claims.

10 The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel* 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or
15 provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

REMARKS

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP 706.07(a). Applicant is reminded of the
20 extension of time policy as set forth in 37 CFR § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

25 A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37

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CER § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

5 Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson, whose telephone number is (703)-308-3978. The examiner can normally be reached on Monday-Thursday from 7:00 a.m. to 5:30 p.m.

10 If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Moskowitz Parr, can be reached on (703) 308-2454. The fax phone number for this Group is (703)-308-4227.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)-308-0196.

15 
Bradley L. Sisson
Examiner
October 28, 1994


MARGARET PARR
SUPERVISORY PATENT EXAMINER
GROUP 1800